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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,795	08/08/2006	Serge Louis Boulet	X-16400	6451

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ELI LILLY & COMPANY  
PATENT DIVISION  
P.O. BOX 6288  
INDIANAPOLIS, IN 46206-6288

EXAMINER
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O'DELL, DAVID K

ART UNIT	PAPER NUMBER
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1625

NOTIFICATION DATE	DELIVERY MODE
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01/08/2008

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

## Office Action Summary

**Application No.**

10/597,795

**Applicant(s)**

BOULET ET AL.

**Examiner**

David K. O'Dell

**Art Unit**

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 16 and 19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 16 and 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>8 August 2006</u> | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Claims 16 & 19 are pending in the current application.
2. This application is a 371 of PCT/US05/04174 filed 02/11/2005 which claims benefit of 60/548,679 filed 02/27/2004.

#### ***Claim Objections***

Claim 16 is objected to for not depending from a preceding claim.

#### **Claim Rejections – 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 16 & 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stockbroekx et. al. U. S. patent 4,861,785. The claims are drawn to compounds where the heteroaryl is a benzothiazole and R<sup>1</sup> is alkyl. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

#### **Determination of the scope and content of the prior art**

***(MPEP 2141.01)***

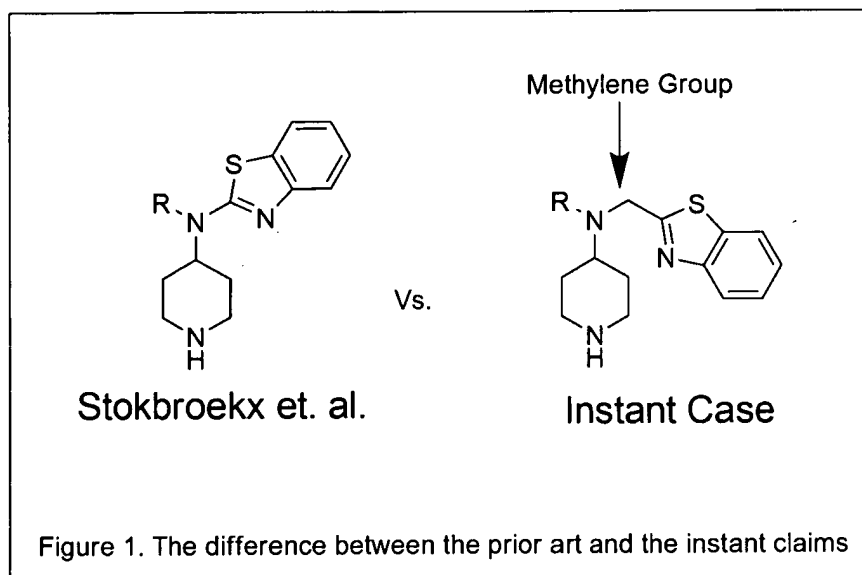
Stockbroekx et. al. teaches two compounds that are analogs of the compounds of the instant case. In particular Stockbroekx et. al. teaches a large number of compounds in the table at column 18,

No.	R	R <sup>1</sup>	A <sup>1</sup> =A <sup>2</sup> -A <sup>3</sup> =A <sup>4</sup>	Z	isomerism	salt/base	mp. (°C.)
69	H	H	CH=CH-CH=CH	S	—	2HBr	260
70	OH	H	CH=CH-CH=CH	S	cis	2HBr.H <sub>2</sub> O	266-300
71	H	H	N=CH-CH=CH	S	—	3HBr	236.9
72	H	CH <sub>3</sub>	N=CH-CH=CH	S	—	base	144
73	H	H	CH=CH-CH=CH	O	—	2HBr	263
74	H	CH <sub>3</sub>	CH=CH-CH=CH	O	—	2HBr.12H <sub>2</sub> O	261.2
75	H	CH <sub>3</sub>	CH=CH-CH=CH	O	—	base	130.3
76	H	C <sub>2</sub> H <sub>5</sub>	CH=CH-CH=CH	S	—	*	197.7
77	H	n-C <sub>4</sub> H <sub>9</sub>	CH=CH-CH=CH	S	—	**	160.0
78	H	CH <sub>3</sub>	CH=C(CH <sub>3</sub> )-CH=CH	S	—	base	74.3
79	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	CH=CH-CH=CH	S	—	*	206.4
80	OCH <sub>3</sub>	CH <sub>3</sub>	CH=CH-CH=CH	S	cis	(COOH) <sub>2</sub>	206.4
81	H	CH <sub>3</sub>	CH=CH-CF=CH	S	—	2HCl.H <sub>2</sub> O	266.4
82	H	CH <sub>3</sub>	CH=CF-CH=CH	S	—	base	—
83	H	CH <sub>3</sub>	CH=CH-C(OH)=CH	S	—	2HBr	—
84	H	i-C <sub>3</sub> H <sub>7</sub>	CH=CH-CH=CH	S	—	*	181
85	H	CH <sub>3</sub>	CH=CH-C(OCH <sub>3</sub> )=CH	S	—	base	—
86	H	CH <sub>3</sub>	CH=CH-C(Cl)=CH	S	—	*	158
87	H	CH <sub>3</sub>	C(Cl)=CH-CH=CH	S	—	base	—
88	H	CH <sub>3</sub>	CH=C(OH)-CH=CH	S	—	2HBr	—
89	H	CH <sub>3</sub>	CH=C(Cl)-CH=CH	S	—	2HCl.H <sub>2</sub> O	237.8

The compounds 69, 76, 77, 78, 81, 82, 84, 86, 87, 89 teach N-alkylated amino-piperidinyl benzothiazoles with methyl, ethyl, isopropyl, and butyl groups for R<sup>1</sup>, in addition to halo substitution on the benzothiazole.

***Ascertainment of the difference between the prior art and the claims***

It is clear that the prior art differs only in the presence of a methylene group between the amino group and the benzothiazole. This relationship is illustrated graphically in Figure 1 for convenience.



***(MPEP 2141.02)***

**Finding of prima facie obviousness**

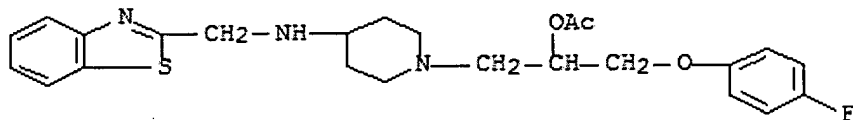
***Rational and Motivation***

***(MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Stokbroekx et. al. to produce the instant invention. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would

be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to insert a methylene at the point of attachment in order to increase potency. See *In re Coes, Jr.* (CCPA 1949) 173 F2d 1012, 81 USPQ 369. Moreover the compounds of Stokbroek were used as intermediates in the synthesis of other N-piperidinyl-alkylated compounds, one of which appears to contain a methylene group (shown below):

RN 106185-76-6 CAPLUS  
CN 1-Piperidineethanol, 4-[(2-benzothiazolylmethyl)amino]-.alpha.-[(4-fluorophenoxy)methyl]-, acetate (ester) (9CI) (CA INDEX NAME)



A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL

1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

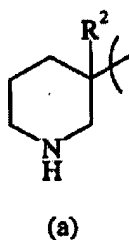
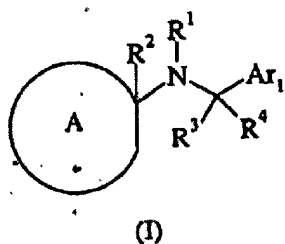
### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 16 & 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 4, 5, 12-14, 22 of copending Application No. 10/558,588. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '588 application embrace position isomers of the compounds of the instant claims. When the variable definitions of claim 1 are as shown below:



R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each independently selected from hydrogen

Ar<sub>1</sub> is selected from:

a 5- membered monocyclic heteroaromatic group

these compounds differ only from the instant case in the position of the amino group on the piperidine ring.

Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ulliot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way,



obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

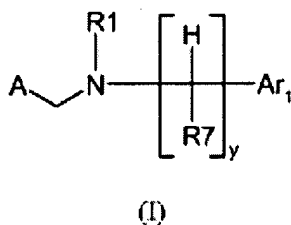
*In re Surrey* 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...". *Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents*, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* (CONH<sub>2</sub>) and *ortho* (OCH<sub>3</sub>) obvious over a dye with the same nucleus and *meta* (CONH<sub>2</sub>) and *para* (OCH<sub>3</sub>) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-

methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouché*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). *In re Hass* 60 USPQ 552, which found a *prima facie* case of obviousness of 1-chloro-1-nitrobutane over 1-chloro-1-nitroisobutane taught in the prior art, *Ex parte Ullyot*, 103 USPQ 185, which found a *prima facie* case of of 2-oxo-quinolines obvious over prior art a 1-oxo-isoquinoline, *In re FINLEY*, 81 USPQ 383, 2-ethyl hexyl salicylate over octyl salicylate.

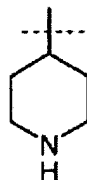
*Ex parte Engelhardt*, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 16 & 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 & 20 of copending Application No. 11/568,641. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '641 application embrace analogs of the compounds of the instant claims. When the variable definitions of claim 1 are as shown below:



wherein  
A is



R1 is C<sub>2</sub>-C<sub>10</sub>alkyl,

C<sub>3</sub>-C<sub>8</sub>cycloalkyl.

R7 is independently at each occurrence selected from H  
y is 1,

Ar<sub>1</sub> is selected from:

a 5-membered monocyclic heteroaromatic group

These compounds differ only in the presence of a methylene group. (see discussion vide supra for the obviousness of this difference).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071.


The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

8. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

**RITA DESAI**  
**PRIMARY EXAMINER**



12/27/07